REMARKS

Claims 23-42 are pending in this application. Claims 1-22 have been cancelled without prejudice. New claims 23-42 do not incorporate new matter. Support for the claims is found at least in claims 1-22, as originally filed, and in the specification at page 9, lines 22-25.

Rejections Under 35 U.S.C. § 102(b)

In Paper No. 15, the Examiner has rejected claims 1, 5-6, 8, and 22 under 35 U.S.C. § 102(b) as being anticipated by Coleman III, et al., eds., Skin resurfacing, pp 217-234, 1998 ("Coleman") and by Pollack, J. Dermatol. Surg. Oncol.,Vol. 16, No. 10, pp. 957-961, October 1990 ("Pollack"), each taken individually. Relying on that portion of Coleman that describes "FIBREL," the Examiner asserts that Coleman teaches an injectable material for soft tissue augmentation in mammals that comprises cross-linked, blood plasma proteins. Similarly, relying on that portion of Pollack that describes "FIBREL," the Examiner states that Pollack teaches an injectable material for soft tissue augmentation that comprises cross-linked, blood plasma proteins which are purified and sterilized.

The applicants respectfully traverse this rejection, and request that it not be applied to new claims 22-42.

A. The Invention

The invention is a material for soft tissue augmentation that can be used to aesthetically correct scars, wrinkles and other similarly depressed, dermal defects. The injectable material of the invention includes cross-linked blood plasma proteins having at least one amide bond. Also contemplated within the scope of the invention is a method of preparing the material, and a method of soft tissue augmentation in which the material is used.

The injectable materials described meet the need in the art for a safe, non-antigenic, non-irritating, longer lasting and aesthetically pleasing injectable material for soft tissue augmentation that is relatively easy to obtain and to manufacture. The injectable materials of the invention are easily injected, and, once injected, are more resistant to degradation by natural proteases, than injectable materials known in the art. These properties are advantageous because the environment in which augmentation devices are most often used, intradermal compartments of human skin, is heavily populated with proteases, as well as components of the immune system that function to degrade most types of conventional tissue augmentation materials.

B. The References Cited by the Examiner.

Coleman teaches a composition for treating wrinkles and scars that contains a mixture of porcine gelatin powder (collagen), sterile saline, and ε-amino caproic acid. This mixture is sold under the tradename "FIBREL." When administered, Coleman teaches that FIBREL may mixed with a patient's plasma prior to injection. Coleman teaches that FIBREL was designed to stimulate collagen production by the patient's own cells at the site of injection. Col. 1:22-23. Coleman also discloses that use of the composition without the addition of the patient's blood plasma is as effective as use of the composition that does contain the blood plasma. In fact, Coleman advises that use of FIBREL without the blood plasma is additionally advantageous as it avoids any chance of inadvertent contamination of the physician or the physician's assistant with the blood plasma mixture during mixing. Col. 1:37-41. Coleman does not teach or suggest that the blood plasma that may be used to reconstitute the FIBREL powder contains blood plasma protein that have any cross-linkages at all, let alone cross-linkages comprising at least one amide bond.

Similarly, the Pollack reference teaches use of FIBREL for the treatment of scars or wrinkles. Pollack teaches that the FIBREL product is "individually reconstituted for each patient treatment session." To accomplish this, a small amount of the patient's plasma is added to a FIBREL, a mixture of highly purified, denatured porcine collagen (gelatin) and ε-amino caproic acid. Pollack teaches that once injected, the gelatin of the FIBREL composition acts as a temporary matrix upon which the blood plasma constituents, such as fibrin, are deposited Pollack teaches that the ε-amino caproic acid is present in FIBREL to inhibit the "digestion of fibrin, by inhibiting the production of fibrolysin." Pollack teaches that FIBREL acts by activating the patient's own fibroblasts, thereby inducing subsequent collagen deposition by those cells. Pollack does not teach or suggest that any of the components of the blood plasma added into the FIBREL composition are cross-linked, or even associated with one another in any manner. Nor does Pollack suggest that the cross-linking of the blood plasma proteins incidentally present in the blood plasma used to reconstitute the FIBREL is either desirable or necessary. Pollack makes clear that it is not the blood plasma proteins that are acting to augment the targeted tissue area, but rather that it is the subsequently deposited collagen, which is secreted by the patient's own cells.

C. Coleman and Pollack Do Not Anticipate the Invention.

To demonstrate that a reference anticipates a claimed invention, the Examiner must show that each element of the claim is present, either expressly or inherently, in the cited reference. M.P.E.P. 2149. Neither of Pollack or Coleman, which each teach the composition FIBREL and use of the same as reconstituted with blood plasma, teaches expressly or inherently each element of the claims.

The claims of the invention are drawn to an injectable material for soft tissue augmentation that comprises cross-linked blood plasma proteins, wherein the cross-linkages comprise at least one amide bond, or methods of tissue augmentation utilizing the same. In contrast, neither Pollack nor Coleman teaches or suggests that FIBREL reconstituted with blood plasma contains blood plasma proteins that have cross-linkages that comprise at least one amide bond.

Coleman and Pollack teach use of a FIBREL composition, which is made of porcine gelatin (a collagen) and ε-amino caproic acid. The FIBREL composition itself does not constitute any blood plasma proteins. As known to one of skill in the art, a collagen is not a blood plasma protein, but is rather any of a group of fibrous proteins that form the main component of connective tissue in mammals. See specification at page 8; Declaration of Rozlyn Krajcik under 37 C.F.R. § 1.132 (hereinafter "Dec.") at ¶ 26. ε-amino caproic acid is not a protein at all.

Further, there is no teaching or suggestion, either expressly or inherently, in Coleman or Pollack that any proteins that may be present in the blood plasma used to reconstitute the FIBREL composition are cross-linked in any manner. There is no factual or technical basis that would have caused a person of skill to believe that the blood plasma used in the reconstitution step described in Pollack or Coleman inherently discloses plasma having amide cross-linked blood plasma proteins. Neither reference discusses or even alludes to any process by which such cross-links would be formed in the collected blood plasma. Dec. at ¶ 26. Neither Coleman nor Pollack teaches that the blood plasma to be used for reconstitution of FIBREL is treated in any way so as to induce, encourage, or facilitate the formation of cross-linkages that include amide bonds. The references merely state that the blood plasma is mixed with the FIBREL powder to reconstitute it, and even that use of blood plasma itself is unnecessary. Dec. at ¶ 25.

Applicants have submitted the Physician Package Insert that accompanies the FIBREL product for the Examiner's review.[1] Dec. at ¶ 20. The Package Insert serves as confirmation that the blood plasma used in the reconstitution of FIBREL as taught in Coleman and Pollack is not treated or otherwise subjected to any processes that would result in the formation of amide bond cross-linkages of any constituent blood plasma proteins, or any other type of cross-linkages. Dec. at ¶ 27.

In fact, one of skill would understand that any formation of linkages in the blood plasma is discouraged. The Package Insert discloses that the anti-coagulant citrate dextrose is added to the blood sample to prevent blood coagulation. Dec. at ¶ 27. Anti-coagulants are known in the art to prevent the cascade of enzyme mediated reactions that result in clotting, *i.e.*, the formation of bonds between various blood proteins. Thus, Pollack and Coleman discloses that the formation of cross-linkages between and among blood plasma proteins is undesirable. Dec. at ¶ 27.

Furthermore, a person of skill in the art upon reading Coleman and Pollack, would understand that there are no amide bonds formed between the blood plasma proteins present in the patient's plasma, as the formation of such bonds does not occur spontaneously and casually in nature. Dec. at ¶ 27-29. This is also illustrated by the examples presented in the patent application itself. Dec. at ¶ 31-36. Attempts at tissue augmentation using blood plasma alone, as seen in Comparative Use Example 1, were unsuccessful, in comparison to tissue augmentation carried out using the composition of the invention. See, Table 1, comparing Comparative Use Example 1 to Use Example 1; Dec. at ¶ 33-35.

Thus, a person of skill in the art upon reading Coleman and Pollack and being familiar with the use and composition of the FIBREL tissue augmentation device reconstituted with a patient's blood plasma, would easily understand that neither Coleman, Pollack, nor the FIBREL composition Product Insert teaches or suggests each element of the invention as claimed, inherently or expressly. Accordingly, for at least these reasons, it is respectfully requested that the Examiner reconsider the § 102(b) rejection, and not apply it to new claims 23-42.

[1] It is also listed in a Supplemental Information Disclosure Statement that is filed simultaneously with this Amendment.

Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-22 under 35 U.S.C. § 103(a), asserting such claims are unpatentble over the disclosure of Coleman or Pollack taken in view of:

1. Grabarek et al., Analytical Biochemistry, Vol. 185, pp. 131-135 (1990) ("Grabarek"); or

2. Wong, Chemistry of Protein Conjugation and Cross-linking, pp. 39-40 and 195-207 (1991) ("Wong"); or

3. Wang, et al., Journal of the Parenteral Drug Assoc., Vol. 34, No. 6, pp. 452-462 (Nov.-Dec. 1980) ("Wang").

The Examiner asserts that Grabarek teaches use of cross-linking agents for the purpose of cross-linking protein-protein complexes, including use of zero-length-cross-linking procedures. Wong, according to the Examiner, teaches various zero-cross-linking reagents for the purpose of creating stable bonds between two intrinsic chemical moieties or one of one or more polypeptide chains. Finally, the Examiner contends that Wang teaches numerous physiologically acceptable fluids as additives for parenteral formulations, including anesthetic compounds. None teaches, discusses, or suggests the use of the disclosed processes or reagents to produce and injectable material for tissue augmentation comprising intermolecular cross-linked blood plasma proteins wherein the cross-linkages comprise at least one amide bond. Thus, the applicants respectfully traverse these rejections and request that it not be applied to new claims 23-42.

The Examiner has failed to meet the requirements to establish a *prima facie* case of obviousness. The disclosures of Coleman and Pollack are described above. Grabarek teaches a two-step procedure for zero-length cross-linking using active esters. Similarly, Wong teaches various zero-cross-linking reagents for the purpose of creating stable bonds between two intrinsic chemical moieties or one of one or more polypeptide chains. Wang teaches physiologically acceptable fluids and additives for parenteral formulations.

The combinations suggested by the Examiner do not teach or suggest each element of the invention, for at least the reasons discussed above in Section I of this response. Specifically, neither Coleman nor Pollack teaches or suggests a tissue augmentation composition comprising cross-linked blood plasma proteins, where such cross-linkages include at least one amide bond. Nor do the disclosures of Grabarek, Wong or Wang remedy this deficiency.

Grabarek does not teach or suggest compositions for use in tissue augmentation,. Additionally, the proteins upon which the two step zero-length cross-linking procedure are practiced are obtained from rabbit back and leg muscles, and are not blood plasma proteins. In Wong, only a general disclosure of zero-length cross-linking procedures is provided, and Wang teaches only use of suitable vehicles and additives for injectable compositions.

Additionally, even if each element of the invention was taught by the combination, which they are not, a person of skill in the art would not have been motivated to make the combination proposed by the Examiner. Both Coleman and Pollack teach use of FIBREL for tissue augmentation. FIBREL, as the references themselves disclose, acts to fill by recruiting fibroblasts which then secrete collagen, which itself then acts as the substance that results in augmentation. No proteins, blood plasma proteins or otherwise, are involved in the augmentation aspect of the composition. This is the reason that, as taught in Pollack, FIBREL is just as effective when used without reconstitution in the patient's plasma. Thus, a person of skill in the art would not have been motivated to take blood plasma proteins, a completely different type of filler from that taught in Coleman and Pollack, and, proteins that are ordinarily soluble and biodegradable within the body, and cross-link them in order to arrive at the present invention.

Finally, a person of skill in the art would not have had a reasonable expectation of success in making the combination of these references, as stated above, Coleman and Pollack teach use of collagen as a filler substance, collagen that is secreted by the patient's own cells. A person of skill in the art would understand that blood plasma proteins, which are normally soluble and biodegradable and do not serve any cell signaling or recruiting function, are not capable of recruiting fibroblasts to enable the secretion of collagen, and the subsequent "filling" of the intradermal skin compartment into which the composition is injected. Thus, a person of skill in the art reviewing Coleman/Pollack and the secondary references, would have had no reasonable expectation that combination of such references would result in a tissue augmentation device that comprises blood proteins which are cross-linked, wherein the cross-linkages include at least one amide bond.

Accordingly, it is respectfully requested that the Examiner reconsider and withdraw the § 103(a) rejection, and not apply the rejection to the new claims.

CONCLUSION

It is respectfully submitted that the applicants have distinguished the pending claims over the art cited by the Examiner. Accordingly, it is respectfully requested that the Examiner consider and allow claims 23-42 at the earliest opportunity, and issue a Notice of Allowance.

Should the Examiner wish to discuss the claims, the art, or any of the issues addressed or raised in this response, he is requested to contact the undersigned at the telephone number given below.

Respectfully submitted,

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9 July 2003 By: Kristyne A. Bullock
(Date)

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